fluoro-3,4-dihydro-2*H*-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate in an appropriate aqueous organic solvent.

18. (twice amended) A process according to claim [15 or] 16 or 17, wherein the aqueous organic solvent is aqueous acetone.

19. (amended) The salt according to claim [2] 3 in [substantially] crystalline form.

20. (amended) A method according to claim 12 for [the prevention or] the treatment of urinary incontinence.

Add the following new claim:

--21. A pharmaceutical formulation according to claim 5 for oral administration.--

REMARKS

Upon entry of the amendments herein, claims 2-5 and 12-21 are pending in the application. Claims 4, 5 and 12-20 have been amended; claims 1 and 11 have been canceled; and new claim 21 has been added.

Applicants took some pains in their previous response to explain to the Examiner that the claims had been amended during the International Stage on September 17, 1998 and that it is the claims in this form that should be the basis for examination in

the U.S. The justification for, and explanation of, Applicants' claim numbering was felt to be necessary because the claim numbering thus far used by the Examiner and by Applicants differs, and this has caused considerable confusion. A further attempt was made to explain the situation to the Examiner during a telephone discussion between the Examiner and Applicants' agent on December 12, 2000.

However, the Examiner asserted that there was no evidence in the PTO file of the September 17, 1998 amendments and, therefore, that the claims as they appeared in the application when it was filed in the U.S., i.e., June 8, 1998, would remain the basis for examination. In the interests of expediting prosecution of the application, Applicants, through their agent, agree to this arrangement.

Applicants' September 17, 1998 Amendment in the International Stage had the effect of canceling original claim 1 and renumbering original claims 2-18 as 1-17, respectively. Thus, in order to render their claim numbering the same as that used by the Examiner, Applicants have herein increased by one the number of each of their claims that remain pending in the application. Accordingly, pending claims 1-4 and 11-19 (by Applicants' numbering) have been renumbered as 2-5 and 12-20, respectively. In concert, the claim dependencies have also been amended, as appropriate. It should be noted that, particularly in those claims which were amended prior to this communication (i.e., those claims now designated as "twice amended" or "thrice amended"), the Examiner should look to Applicants' previous

numbering to determine the state of the claims prior to the present amendment.

Since Applicants' intended list of claims to be prosecuted in the U.S. National Stage did not include original claim 1, said claim has been canceled herein. Applicants had previously canceled claims 6-10; however, these claims corresponded to claims 7-11 by the Examiner's numbering. Accordingly, claim 11 (by the Examiner's numbering) has been canceled herein and new claim 21, identical to the Examiner's claim 6, has been added. Applicants hope that the actions described in this and the preceding paragraph will serve to resolve the confusion.

Claims 3-5, 11-14, 19 and 20 have been rejected under 35 U.S.C. §112, first paragraph as being nonenabled.

Claims 3-5 and 19 are directed to the salts according to the instant invention; however, the Examiner has not made clear what the grounds of rejection are. The Examiner does state that "[T]he breath [sic] of the claimed invention includes several species within the scope of the generic disclosure, with substituents such as, saturated and unsaturated heterocyclics which are further optionally substituted." Applicants do not understand to what the Examiner is referring.

The rejected claims are directed to a <u>single</u> base compound; this compound has a heterocyclic, i.e., benzopyran, core. There are no heterocyclic substituents, saturated or unsaturated; there are 2 (invariant) cyclobutyl moieties which are part of one of the substituents on the core. Neither these carbocyclic

substituents nor any other substituents are further substituted. This rejection should be withdrawn.

With respect to claims 11-14 and 20 (Applicants note that the Examiner, for no apparent reason, has not included claim 15), the Examiner focuses on the concept of using the claimed salt for the "prevention" of diseases. The Examiner further acknowledges that much is understood in the art of "treating" diseases such as those recited in the instant claims. It is Applicants' understanding from this assessment that the deletion of "prevention" from the method claims would be remedial; accordingly, claims 12-15 and 20 have been amended so that they recite methods for "treatment" only of the recited disorders. The cancellation of claim 11 renders moot its rejection.

The Examiner has rejected the method claims for reciting "medical disturbances" or "related medical disturbances." Apparently, the Examiner failed to recognize that Applicants, in their May 8, 2000 Amendment and Response, deleted this language from their claims 11 and 12 (claims 12 and 13 by the Examiner's numbering) and further amended said claims to more clearly recite the disorders to be treated. Applicants again point out that the Examiner has acknowledged the disclosure found on page 3, lines 6-8 of the instant specification as providing support for the method claims with respect to the specifically recited "related medical disturbances."

Nonetheless, claims 12 and 13 have been further amended herein to make it clear that all recited disorders and disturbances have in common that they are mediated by 5-HT_{1A}-

receptor antagonists. Claim 13 has still further been amended to recite a number of the particular CNS disorders disclosed in page 3, lines 3-6 of the instant specification.

Claims 3-5, 12, 13 and 15-19 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite.

Claims 15-18 have been deemed indefinite on the allegation that there is insufficient antecedent basis for the phrase "process for the manufacture of." In the first place, Applicants wish to point out that, by the Examiner's numbering, claim 15 is a method-of-treatment claim; it would appear that the Examiner meant to reject claims 16-18. In any event, claims 16 and 17 have been amended along the lines suggested by the Examiner, and the rejection is now moot.

The terms "CNS" and "5-HT_{1A}" in claims 12 and 13 have been amended along the lines suggested by the Examiner, thus rendering moot the rejection.

Claims 3-5 and 19 have been rejected because of the presence of the phrase "substantially crystalline form" in claims 3 and 19. The Examiner has indicated that deleting the word "substantially" would be remedial, and this amendment has been made. However, for the record, Applicants wish to make the following further clarifications with respect to the forms in which the salt may exist.

The Examiner asserts that Applicants are entitled only to subject matter disclosed in the specification as originally filed and reminds Applicants that the introduction of new matter into the specification is not allowed. In the first place, Applicants

wish to emphasize that the PXRD data presented in their last response are not necessary as support for the claims in their present form but were provided as additional support for the definiteness of said claims.

In any case and furthermore, as pointed out previously by Applicants, the crystalline form of the salt is disclosed to be the preferred form and thus, certainly, not the only form of the salt according to the invention. Applicants do not disagree with the Examiner's general statement that only originally disclosed subject matter is patentable. However, the Examiner has provided no support for his contention that the instant disclosure of the crystalline form as preferred does not constitute disclosure that the salt may exist in other forms as well. Further, the Examiner has not provided reasonable basis for contending that the salts must be assumed to be in crystalline form only.

Applicants further wish to reemphasize that the claims do not recite any specific salt forms that are not literally disclosed in the specification. Applicants are simply claiming the salt, without further limitation, in the base claims and, then, in dependent claims, claiming the disclosed preferred embodiment of the salt in crystalline form. Thus, the present pattern of the claims, i.e, independent base claims directed to the salt followed by claims dependent therefrom reciting the further limitation that the salt is in crystalline form, is a normal and acceptable one based on the disclosure of the instant specification. The claimed subject matter with respect to the salts must be seen as subject matter that is disclosed in the

specification as originally filed. The Examiner is also reminded that the claims themselves as originally filed are to be considered as part of the original disclosure of patentable subject matter.

The Examiner has maintained the rejection of claims 1-5 and 12-18 as being obvious over International Publication WO 95/11891 of Evenden, et al. From the Examiner's perspective, Applicants' previous arguments that they have selected a single base compound and a particular salt thereof from among the very large number of possibilities presented by Evenden are not persuasive. The Examiner maintains that the instant invention represents "an indiscriminate selection of 'some' among 'many'" (in seeming contradiction to the Examiner's expressed view (see below) that Evenden does not even disclose "many" possibilities in the first place). The Examiner thus maintains that the decision of In re Lemin 141 USPQ 814 is more appropriate to the present situation than either the decision of In re Ruschig 154 USPQ 118 or In re Jones USPQ2d 1941. However, the Examiner has misassessed the situation and misinterpreted Applicants' previous arguments.

In the first place, regardless of how many compounds are disclosed by Evenden, it cannot be said that the instant invention, a particular salt of a single base compound, is an "indiscriminate" selection from among the possibilities. As is clear from the disclosure in the instant specification, Applicants had a particular goal, and in their selection process they discovered, without the benefit of any prior suggestion,

that the tartrate salt of the disclosed base compound was superior to other salts in meeting that goal.

Furthermore, contrary to the Examiner's assertion, Applicants have not stated that Evenden discloses a total of 44 compounds. What Applicants stated, and what is true, is that they "have discovered a single base compound from among all of those encompassed by Evenden formula I and have further selected the tartrate salt, in particular the monohydrate, of said base compound from among the 44 salts listed in the Evenden disclosure." An inspection of the reference cited by the Examiner reveals that formula I, in view of the variability of substituents R_1, R_2 and R_4, encompasses twenty base compounds (see, e.g., page 5, lines 1-19). Then, on page 7, lines 5-16, are listed 44 acids which can be used in the formation of pharmaceutically acceptable acid addition salts of any and all of the base compounds of formula I. Thus, the total number of possibilities disclosed by Evenden is, minimally, 20 x 44 = 880; Applicants have selected one from among this very large list of possibilities.

Applicants thus reiterate their assertion that, in the first place, the present invention is not an indiscriminate selection. Furthermore, not only is the selection not indiscriminate but it cannot be said to be a selection of some among many. The invocation of In re Lemin is not appropriate in this case; more appropriately, as previously asserted, In re Ruschig and/or In re Jones could be invoked. Based on his erroneous tally of 44 possibilities disclosed by Evenden, the Examiner concludes that

it would have been routine to make and screen such a limited number of compounds to determine their relative properties. However, as pointed out above and as can readily be seen from the Evenden disclosure, the number of possibilities is far greater than that appreciated by the Examiner. The making and screening of the possibilities in order to arrive at the instant invention cannot be said to be routine, nor can the selection of a single base compound and a particular salt thereof from among all the possibilities properly be assessed as obvious.

Applicants further note that the Evenden reference was cited during examination of the International Application of which the instant application is the National Stage. In the International Search Report, the Evenden reference is listed as a "category A" reference, i.e., a "document defining the general state of the art which is not considered to be of particular relevance." This assessment was reiterated in the International Preliminary Examination Report.

Accompanying this response is a Supplemental Information Disclosure Statement disclosing a new reference that has just come to Applicants' attention. The priority date of the instant application is earlier than the publication date of the new reference; nonetheless, Applicants would like to have this reference made of record in the instant application.

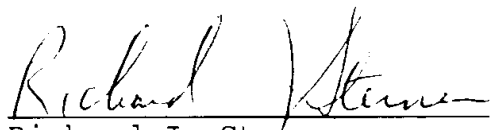
In view of the amendments herein to the claims and the arguments set forth above, the claimed subject matter meets the requirements of enablement and definiteness and is patentably distinct over the cited prior art. Reconsideration and allowance

of pending claims 2-5 and 12-21 are respectfully requested. Should any other matter require attention prior to allowance of the application, it is requested that the undersigned be contacted.

The Assistant Commissioner is hereby authorized to charge any fee which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: December 20, 2000

Respectfully submitted,



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Enclosures